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Application No. 10/650,592  
Amendment dated May 5, 2008  
Reply to non-Final Office Action of February 5, 2008

Docket No.: COTH-P01-001

**AMENDMENT TO THE CLAIMS**

- 1-4. (Canceled)
5. (Currently Amended) An adzyme for enzymatically altering a substrate, the adzyme being a fusion protein comprising: a protease domain that cleaves at least one peptide bond of said substrate to produce one or more products, and a polypeptide targeting domain that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, wherein
- wherein said targeting domain and said protease domain are discrete and heterologous with respect to each other,
- said targeting domain, when provided separately, binds to the substrate, and is selected from the group consisting of: an antibody or a functional fragment thereof, a polypeptide comprising an antigen binding site of the antibody, a polypeptide engineered based on a protein scaffold, and a polypeptide engineered to bind to the substrate,
- said protease domain, when provided separately, cleaves at least one peptide bond of said substrate to produce one or more products, and
- wherein the substrate is an insoluble protein-containing aggregate ~~a biomolecule in a biomolecular accretion.~~
6. (Canceled)
7. (Previously Presented) The adzyme of claim 5, wherein the substrate is endogenous to a human patient.
8. (Previously Presented) The adzyme of claim 7, wherein the adzyme is effective against the substrate in the presence of physiological levels of human serum protein.
9. (Previously Presented) The adzyme of claim 8, wherein the human serum protein is human serum albumin.
- 10-25. (Canceled)
26. (Previously Presented) The adzyme of claim 5, wherein said fusion protein includes a linker between said protease domain and said targeting domain.

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27. **(Previously Presented)** The adzyme of claim 26, wherein said linker is an unstructured peptide.
28. **(Canceled)**
29. **(Original)** The adzyme of claim 27, wherein said linker includes one or more repeats of Ser<sub>4</sub>Gly or SerGly<sub>4</sub>.
30. **(Canceled)**
31. **(Previously Presented)** The adzyme of claim 26, wherein said linker is selected to provide steric geometry between said catalytic domain and said targeting domain such that said adzyme is more active than said catalytic domain or targeting domain with respect to the reaction with said substrate.
- 32-34. **(Canceled)**
35. **(Previously Presented)** The adzyme of claim 5, wherein the fusion protein is a cotranslational fusion protein encoded by a recombinant nucleic acid.
36. **(Canceled)**
37. **(Currently Amended)** The adzyme of claim 5, wherein the ~~biomolecule~~ substrate is produced by a cell.
- 38-47. **(Canceled)**
48. **(Currently Amended)** The adzyme of claim 5, wherein the substrate is biomolecular ~~accretion is selected from among:~~ an amyloid deposit ~~or~~ and an atherosclerotic plaque.
49. **(Currently Amended)** The adzyme of claim 5, wherein the substrate biomolecular ~~accretion~~ is produced by a pathogen.
50. **(Previously Presented)** The adzyme of claim 49, wherein the pathogen is a protozoan, a fungus, a bacterium, or a virus.
51. **(Currently Amended)** The adzyme of claim 5, wherein the substrate biomolecular ~~accretion~~ comprises a prion protein.
- 52-55. **(Canceled)**

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56. (Withdrawn) The adzyme of claim 5, wherein said protease is a zymogen.
57. (Canceled)
58. (Previously Presented) The adzyme of claim 5, wherein said adzyme is purified from a cell culture in the presence of a reversible protease inhibitor.
- 59-68. (Canceled)
69. (Previously Presented) The adzyme of claim 5, wherein the adzyme is resistant to cleavage by the protease domain at an adzyme concentration that is about equal to the concentration of adzyme in a solution to be administered to a subject.
70. (Currently Amended) The adzyme of claim 5, wherein said adzyme alters the half-life of the substrate biomolecule *in vivo*.
71. (Canceled)
72. (Currently Amended) The adzyme of claim 5, wherein said adzyme alters the distribution of the substrate biomolecule *in vivo*.
73. (Canceled)
74. (Currently Amended) The adzyme of claim 5, wherein said adzyme reduces a biological activity of said substrate biomolecule.
75. (Canceled)
76. (Currently Amended) The adzyme of claim 5, wherein said substrate biomolecule binds a plurality of different molecules *in vivo*, and said adzyme alters the binding specificity of said substrate biomolecule.
77. (Canceled)
78. (Currently Amended) The adzyme of claim 5, wherein said adzyme alters the interaction of said substrate biomolecule with other molecules *in vivo*.
- 79-107. (Canceled)

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108. **(Currently Amended)** The adzyme of claim 5 [[107]], wherein the targeting domain is selected from the group consisting of a monoclonal antibody, an Fab and F(ab)<sub>2</sub>, an scFv, a heavy chain variable region and a light chain variable region.
109. **(Canceled)**
110. **(Withdrawn)** The adzyme of claim 5, wherein said targeting domain is an artificial protein or peptide sequence engineered to bind to said substrate.
- 111-116. **(Canceled)**
117. **(Previously Presented)** The adzyme of claim 5, wherein the protease is selected from among: MT1-MMP; MMP12; tryptase; MT2-MMP; elastase; MMP7; chymotrypsin; and trypsin.
- 118-126. **(Canceled)**
127. **(Previously Presented)** An adzyme preparation for therapeutic use in a human patient, the preparation comprising an adzyme of claim 5.
128. **(Original)** The adzyme preparation of claim 127, further comprising a pharmaceutically effective carrier.
129. **(Original)** The adzyme preparation of claim 127, wherein the adzyme preparation is formulated such that autocatalytic modification of the adzyme is inhibited.
130. **(Canceled)**
131. **(Previously Presented)** The adzyme preparation of claim 127, further comprising a reversible inhibitor of said protease.
132. **(Original)** The adzyme preparation of claim 131, wherein the reversible inhibitor is safe for administration to a human patient.
133. **(Original)** The adzyme preparation of claim 127, wherein said adzyme preparation is substantially pyrogen free.
134. **(Original)** The adzyme preparation of claim 127, wherein said adzyme preparation is packaged with instructions for administration to a patient.

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135. **(Withdrawn)** A method of making a medicament for use in treating a disorder that is associated with an activity of the substrate of an adzyme of claim 5, the method comprising formulating the adzyme for administration to a human patient.
136. **(Canceled)**
137. **(Withdrawn)** A method of treating a disorder that is associated with an activity of the substrate of an adzyme of claim 5, the method comprising administering a therapeutically effective dose of the adzyme to a human patient in need thereof.
- 138-146. **(Canceled)**
147. **(Withdrawn)** A method for manufacturing an adzyme, the method comprising
- a) culturing a cell comprising an expression vector comprising a nucleic acid encoding the adzyme of claim 5, in conditions that cause the cell to produce the adzyme; and
  - b) purifying the adzyme to substantial purity.
- 148-149. **(Canceled)**
150. **(Withdrawn)** The method of claim 147, wherein the purifying the adzyme to substantial purity includes the use of a reversible inhibitor that inhibits autocatalytic activity of the catalytic domain.
- 151-155. **(Canceled)**
156. **(Previously Presented)** The adzyme of claim 5, wherein the targeting moiety comprises a polypeptide or polypeptide complex.
157. **(Previously Presented)** The adzyme of claim 5, wherein the adzyme is resistant to autocatalysis.